PCT W INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A23L 1/305, A61K 31/195, 31/70, 38/28 — A1

(11) Internati nal Publication Number: WO 96/18313

(43) International Publication Date: 20 June 1996 (20.06.96)

(21) International Application Number: PCT/GB95/02933

(22) International Filing Date: 15 December 1995 (15.12.95)

(30) Pri rity Data:

9425514.8	17 December 1994 (17.12.94)	GB
9517443.9	25 August 1995 (25.08.95)	GB

(71) Applicant *(for all designated States except US)*: THE UNIVERSITY OF NOTTINGHAM [GB/GB]; University Park, Nottingham NG7 2RD (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GREENHAFF, Paul, Leonard [GB/GB]; The University of Nottingham, University Park, Nottingham NG7 2RD (GB). GREEN, Allison, Lesley [GB/GB]; The University of Nottingham, University Park, Nottingham NG7 2RD (GB). MACDONALD, Ian, Andrew [GB/GB]; The University of Nottingham, University Park, Nottingham NG7 2RD (GB). HULTMAN, Eric [SE/GB]; The University of Nottingham, University Park, Nottingham NG7 2RD (GB).

(74) Agent: SKINNER, Michael, Paul; Swindell & Pearson, 48 Friar Gate, Derby DE1 1GY (GB).

(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published

With international search report.

(54) Title: INCREASING CREATINE AND GLYCOGEN CONCENTRATION IN MUSCLE

(57) Abstract

Methods and compositions for increasing creatine retention in, and glycogen concentrations in muscle of, the human and/or animal body, comprising increasing the creatine concentration in blood plasma of a body and causing a substantially simultaneous increase in blood plasma insulin concentration. Compositions comprising creatine or an active derivative thereof are introduced into the body, by oral ingestion or infusion, such as injection, along with a carbohydrate, such as glucose to augment insulin release into the blood which in turn drives glucose into muscle for glycogen synthesis. Insulin or an active derivative thereof may also be comprised in the composition either along with or instead of the carbohydrate.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

Increasing Creatine and Glycogen Concentration in Muscle

The present invention concerns the retention of creatine within the body, and relates in particular but not exclusively to a method and composition for increasing creatine uptake in humans. The invention also concerns a method and composition for simultaneously increasing glycogen concentration in muscle.

Creatine (methylglycocyamine, $H_2NC{=}NH.N(CH_3)CH_2CO_2H$) is known to be present in the muscles of vertebrates. It is present in a phosphorylated and a non-phosphorylated form and has been shown to be involved in muscular contraction and the development of fatigue. Creatine is produced naturally by the body, but is also obtained from animal foods.

Most bodily creatine is present in muscle, and it is believed that increasing the amount of creatine within muscle favourably affects muscular performance and the amount of work which can be done by the muscle. Accordingly, it is held desirable to be able to influence creatine retention in the body.

Glycogen, $(C_6H_{10}O)x$, is a carbohydrate found in animal cells and is convertible from and to glucose. Athletes endeavour to increase muscle glycogen content before competing in order to enhance muscle performance.

In this specification the term "active derivative" means anything derived from or a precursor of the relevant substance that acts in the same or similar way in the body to the substance, or which is processed into the substance when placed into the body. The terms serum and plasma can be interchanged.

According to the invention there is provided a method of increasing creatine retention in the human or animal body by causing an increase in blood plasma creatine concentration and causing a substantially simultaneous increase in blood plasma insulin concentration.

The plasma creatine concentration may be increased by ingestion and/or infusion of creatine or an active derivative thereof.

The plasma insulin concentration may be increased by infusion of insulin or an active derivative thereof and/or by the ingestion of an agent operable to cause an increase in the blood plasma insulin concentration.

The agent may be a carbohydrate or an active derivative thereof, preferably a simple carbohydrate. Preferably the carbohydrate is glucose.

Preferably the method comprises the simultaneous ingestion of creatine and an agent operable to cause an increase in the blood plasma insulin concentration substantially simultaneously with the arrival in the plasma of the creatine.

The creatine and/or the agent is preferably orally ingested.

The invention further provides a method of increasing glycogen storage, and particularly glycogen concentration in muscle of the human or animal body by causing an increase in blood plasma carbohydrate concentration and insulin concentration and causing a substantially simultaneous increase in blood plasma creatine concentration.

The plasma creatine concentration may be increased by ingestion and/or infusion of creatine or an active derivative thereof. The plasma carbohydrate, which is desirably glucose and insulin concentrations may be increased by ingestion of carbohydrate or an active derivative thereof, but desirably glucose and/or any

other simple carbohydrate and/or by infusion of a carbohydrate or an active derivative thereof, such as glucose or any other simple carbohydrate.

Preferably creatine or an active derivative thereof and glucose and/or another simple carbohydrate are orally ingested.

According to the invention there is further provided a composition for increasing creatine retention in the human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof.

Preferably the composition is in the nature of a dietary supplement.

Preferably the carbohydrate is glucose and/or another simple carbohydrate.

The composition preferably comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

According to the invention there is also provided a method of increasing creatine retention in the human or animal body by ingestion and/or injection of a

composition as hereinbefore described. Preferably the composition is ingested in an amount of 100 g to 700 g per day, which may be taken in four equal parts throughout the day.

Further according to the present invention there is provided a composition for increasing creatine retention in the human or animal body, the composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof.

Further according to the present invention there is provided a composition for increasing glycogen storage in the human or animal body and particularly glycogen concentration in muscle, the composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof.

The composition may be in a form to be ingested and/or injected into the body.

According to the invention there is also provided a method of increasing creatine retention in the human or animal body by ingestion and/or injection of a composition as described above.

According to a further aspect of the invention

there is provided a method increasing glycogen storage in the human or animal body and particularly glycogen concentration in muscle by ingestion and/or injection of a composition as described above.

Preferably a carbohydrate, or an active derivative thereof, is also ingested and/or injected desirably such that an increase in blood plasma carbohydrate concentration and insulin concentration occurs substantially simultaneously with an increase in blood plasma creatine concentration.

According to the invention there is also provided a composition for increasing glycogen storage in the animal or human body and particularly glycogen concentration in muscle of the human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof.

Preferably the composition is in the nature of a dietary supplement.

Preferably the carbohydrate is glucose and/or another simple carbohydrate.

The composition preferably comprises 2 to 8% by

weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

According to the invention there is also provided a method of increasing glycogen storage in the human or animal body and particularly glycogen concentration in muscle by ingestion and/or injection of a composition as hereinbefore described.

Preferably the composition is ingested in an amount of 100 g to 700 g per day, which may be taken in four equal parts throughout the day.

According to the invention there is further provided a composition comprising creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use as an active pharmaceutical composition.

The invention also provides a composition comprising creatine or an active derivative thereof and insulin or an active derivative thereof for use as an active pharmaceutical preparation. The composition may also comprise a carbohydrate or an active derivative thereof.

The invention further provides creatine or an

active derivative thereof and a carbohydrate or an active derivative thereof for use in the manufacture of a substance for increasing creatine retention in the human or animal body.

The invention also provides a composition comprising creatine or an active derivative thereof, and insulin or an active derivative thereof, for use in the manufacture of a substance for increasing creatine retention and/or glycogen storage in the human or animal body, such as muscle. Carbohydrate or an active derivative thereof may also be provided.

The invention further provides a composition comprising creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use in the manufacture of a substance for increasing glycogen concentration in muscle of the human or animal body.

Preferably the carbohydrate is glucose and/or another simple carbohydrate.

The composition preferably comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

The methods and compositions of the invention may be used to increase bodily creatine retention in humans. This is desired, for example, by sportsmen and athletes to avoid or delay the onset of muscular fatigue. The ability to increase creatine retention may also be desired in individuals having relatively low general creatine levels, for example vegetarians who do not take animal protein, and sufferers of disease which affects muscle. The present invention enables creatine retention to be increased to a greater extent than is achieved by making creatine available to the body alone.

The invention also permits the increase of muscle glycogen concentration. This is desired by athletes to enhance performance. Also, increasing the glycogen concentration in muscle is of interest where insulin sensitivity of the body is impaired by, for example, obesity, diabetes, heart failure or post-surgical trauma.

The invention will be further described for the purposes of illustration only with reference to the following examples and to the drawings, in which:-

Fig. 1 is a graph showing increase in total creatine concentration against change in glycogen concentration in subjects of group A of Example 2;

Fig. 2 is a similar graph for subjects of group B of Example 2;

Fig. 3 is a graph showing serum insulin concentration against time for all groups in Example 4; and

Fig. 4 is a graph showing blood plasma glucose concentration against time, for all groups in Example 4.

Example 1

Experimental

16 men were randomly divided into groups 1 (6 members), 2 (6 members) and 3 (4 members). On day one, fasted subjects gave a blood sample and then consumed the following preparations:

Group 1 - 5 g creatine in 250 ml low calorie hot orange

Group 2 - 5 g creatine in 250 ml low calorie hot orange plus 500 ml of a glucose drink (LUCOZADE (TM) manufactured by Smith Kline Beecham), containing 90-100 g simple sugars.

Group 3 - 250 ml of low calorie hot orange

Arterialized-venous blood samples were then obtained at 20 minute intervals for the next 4½ hours, while subjects remained in a supine position. For the remainder of the day, and throughout day two, subjects ingested the mentioned preparations at 4 hourly intervals, representing a total daily creatine dose of 20 g. On the morning of day three the subjects reported back to the laboratory and underwent the same procedures as on the first day. All subjects weighed and recorded their dietary intake throughout the study, subjects in group 2 consuming a prescribed high carbohydrate diet, and undertook 24 hour urine collections on day one and day three. Plasma and urine creatine were measured using high performance liquid chromatography and serum insulin was measured using a radioimmunoassay technique.

Results

The results are shown in Table 1, in which CR = creatine. Plasma creatine concentration (u mol/l) was plotted against time for each group, and the area under each curve was determined. Urinary creatine (g) and peak serum insulin (mIU/l) were also determined.

Plasma creatine concentrations peaked within 90 minutes of creatine ingestion and declined towards resting values during the remaining 180 minutes of the

4½ hour period. The area under the plasma creatine curve was lower in group 2 than in group 1, as was urinary creatine content. Following carbohydrate ingestion, serum insulin levels peaked within 30 minutes in group 2 and returned to the pre-ingestion concentration over the remaining 240 minutes. Plasma insulin concentration did not change in group 1 or group 3 over the course of the experiment.

Table 1

Day 1

	Group 1		Group 2	
	Mean	SE	Mean	SE
Area under plasma CR (umol/l/min)	2834.1	298.1	883.9^{++}	109.9
Urinary CR (g)	9.5	1.2	5.0*	0.8
Peak serum insulin (mIU/l)	7.8	1.3	72.0^{++}	11.2

Day 3

	Group 1		Group 2	
	Mean	SE	Mean	SE
Area under plasma CR (umol/l/min)	2637.5	228.6	948.3*	454.5
Urinary CR (g)	11.9	1.1	5.7+	1.2
Peak serum insulin (mIU/l)	9.5	2.0	84.2++	11.5

*$P < 0.05$; +$P < 0.01$; ++$P < 0.001$ - significantly different from corresponding value.

The reduced area under the plasma creatine curve and the lower urinary creatine content of those subjects which had ingested creatine and carbohydrate compared with those which had ingested only creatine shows that bodily uptake of creatine is greater in the second group. This increase in creatine uptake is believed to be insulin mediated, the plasma insulin concentration being increased by the ingested carbohydrate.

Example 2

Experimental

A muscle biopsy sample was taken from the vastus lateralis muscle of each of 21 healthy males and was frozen in liquid nitrogen for subsequent biochemical analysis. Beginning the following day, 12 subjects (group A) each ingested 5 g of creatine dissolved in hot sugar-free orange juice, four times a day for 5 days. The remaining 9 subjects (group B) proceeded as group A, but in addition consumed 500 ml of LUCOZADE, 30 minutes after each creatine preparation had been ingested. Subjects returned the day after the 5th day of supplementation and further muscle biopsy samples were taken. 24 hour urinary collections were made prior to the first biopsy sample (control) and on the first day of creatine supplementation (day 2). Urinary creatine content (in grams) was then measured using high performance liquid chromatography.

Results

Table 2 shows the muscle concentration (mmol/kg dry mass, mean $\pm$ S.E.M.) of phosphorylated creatine (PCr) non-phosphorylated creatine (Cr) and total creatine (TCr) before and after creatine

supplementation. Significant differences between the groups are indicated by an asterisk $p < 0.05$.

Table 2

PCr

	Before Creatine Supplementation	After Creatine Supplementation
Group A	85.1±2.5	92.4±2.1
Group B	84.4±3.8	99.4±2.6*

Cr

	Before Creatine Supplementation	After Creatine Supplementation
Group A	36.4±1.7	49.8±1.5
Group B	39.0±2.3	57.1±3.4*

TCr

	Before Creatine Supplementation	After Creatine Supplementation
Group A	121.5±3.1	142.2±2.6
Group B	123.4±4.3	156.4±5.4*

The increase in total creatine concentration after supplementation in group B was approximately 60% greater than that in group A. This increase comprises increases in both phosphorylated and non-phosphorylated creatine. Urinary creatine content was greater in group A than in group B on day 2 but there was no difference between the groups on the control day.

These results indicate that carbohydrate ingestion increases uptake of creatine in muscle in man, and to a far greater extent than to that seen when creatine alone is ingested.

Example 3

The muscle samples obtained in the study of Example 2 were additionally analysed for muscle glycogen concentration. Muscle samples from a further group C containing 8 subjects were also analysed. This group has followed a similar regime to groups A and B but ingested a preparation of carbohydrate but no creatine, in the form of 500 ml LUCOZADE, at same times as subjects of Groups A and B.

Table 3 shows the muscle concentration (mmol/kg) of glycogen before and after supplementation, and also the difference in the concentration.

Table 3

sd = standard deviation, se = standard error

Group A

	before supplementation	after supplementation	difference
mean	364.8	366.1	1.2
sd	63.4	65.8	67.9
se	19.1	19.8	20.5

Group B

mean	331.1	488.7	157.6
sd	32.5	125.4	126.8
se	10.8	41.8	42.3

Group C

mean	337.5	413.3	75.8
sd	37.3	55.9	33.2
se	13.2	19.8	11.7

Table 3 shows that the mean glycogen difference after supplementation in Group A, who took creatine

only, was very small.

The subjects of Group C, who took glucose only, showed an increase in muscle glycogen concentration after supplementation. However, a more marked increase in muscle glycogen concentration was shown by Group B, who took creatine and glucose together. The results of individual subjects in Group B varied greatly. However, referring to Fig. 2 it is shown that there was a linear relationship between the increase in creatine concentration and the increase in glycogen concentration in subjects of this group, showing a synergistic effect. No such relationship was observed in the subjects in Group A, who ingested only creatine (Fig. 1).

Example 4

Experimental

Twenty nine fasted subjects were divided randomly into three groups, group A (12 subjects), group B (9 subjects) and group C (8 subjects). Each member of group A ingested 5g of creatine dissolved in hot sugar-free orange juice. Each member of group B ingested 5g of creatine dissolved in hot sugar-free orange juice along with 500ml of LUCOZADE, 30 minutes after the creatine preparation had been ingested. Group

C ingested 500ml of LUCOZADE alone.

Arterialised-venous blood samples were obtained from each member of each group before ingestion and at 20 minute intervals immediately following ingestion for the following 220 minutes, while subjects remained in a supine position. Blood serum insulin concentration was measured in each sample, and the results are shown in Table 4 below. Serum insulin concentration (mIU/ℓ) was plotted against time (mins) for each group and is shown in Fig. 3.

The whole blood glucose concentration was also measured before ingestion and at 20 minute intervals for the following 280 minutes and the results obtained are shown in Table 5 below. Whole blood glucose (mmol/ℓ) was plotted against time (mins) for each group and is shown in Fig. 4.

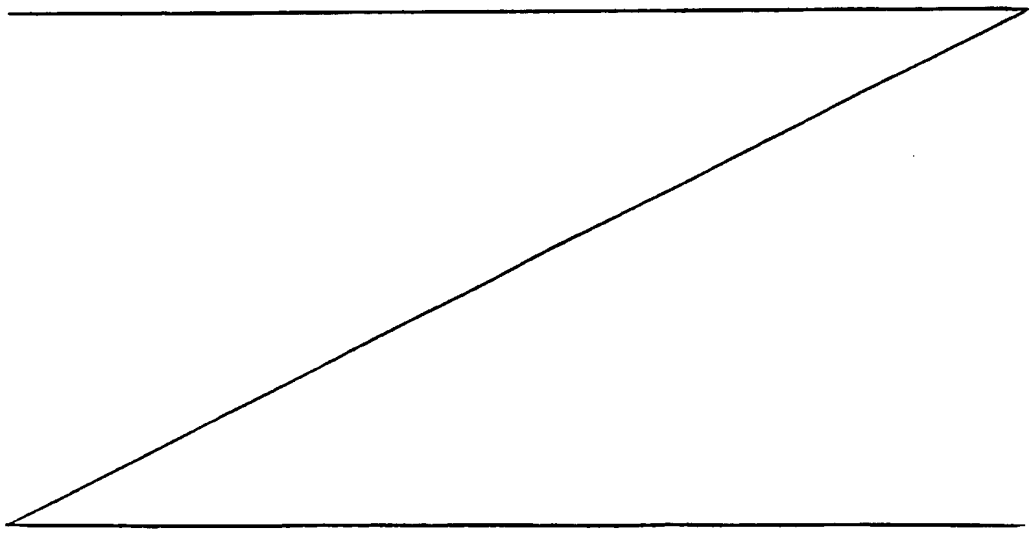


Table 4. Plasma Insulin (mIU/l, mean ± SEM)

Gp	Time (min)	0	20	40	60	120	220
A	Creatine	5.8±0.8	7.3±1.2	6.5±1.0	6.3±1.6	4.7±0.3	4.7±0.4
B	Creatine + carbohydrate	8.8±1.5	87.6±11.1	90.2±20.4	60.8±12.1	15.6±5.2	5.8±0.5
C	Carbohydrate	8.0±1.5	87.6±11.1	90.2±20.4	60.8±12.1	15.6±5.2	5.8±0.5

Table 5. Plasma Glucose (mmol/l, mean ± SEM)

Gp	Time(min)	0	20	40	60	80	100
A	Creatine	4.6±0.2	4.5±0.1	4.5±0.1	4.5±0.1	4.4±0.1	4.2±0.1
B	Creatine + carbohydrate	4.8±0.2	8.5±0.3	7.9±0.2	6.6±0.1	5.8±0.5	5.7±0.3
C	Carbohydrate	4.7±0.2	8.4±0.2	8.2±0.2	7.7±0.1	6.9±0.0	6.7±0.1

Gp	Time (min)	120	140	160	180	200	220	240	280
A	Creatine	4.4±0.2	4.4±0.1	4.3±0.1	4.2±0.1	4.2±0.1	4.2±0.2	4.3±0.1	4.3±0.1
B	Creatine + carbohydrate	4.8±0.2	4.5±0.1	4.1±0.1	4.3±0.2	4.3±0.2	4.2±0.2	4.6±0.2	4.2±0.1
C	Carbohydrate	5.8±0.1	5.3±0.3	4.6±0.2	4.2±0.1	4.0±0.2	4.1±0.2	4.3±0.1	4.4±0.1

The results shown in Table 4 and Fig. 3 clearly show that when creatine is ingested along with carbohydrate (group B), the serum insulin concentration is considerably greater than that found when creatine (group A) and carbohydrate (group C) are ingested alone.

Further, the results shown in Table 5 and Fig. 4, clearly show that when creatine and carbohydrate (group B) are ingested together, there is a considerably more rapid decline in blood plasma glucose concentration, than when carbohydrate is ingested alone. This is a direct result of the augmented release of insulin into the blood caused by the ingested creatine and glucose composition.

This rapid decline in blood plasma glucose concentration is indicative of an increased uptake of glucose into muscle for glycogen synthesis (as seen in Example 3). In other words, the ingestion, or infusion, of creatine in conjunction with carbohydrate increases muscle glycogen storage.

Modifications may be made within the scope of the invention. In particular the carbohydrate may be varied. for example by the use of another simple carbohydrate such as a di-or trisaccharide, although glucose is preferred because of the rapidity with which it enters the bloodstream after ingestion, causing

substantially simultaneous peaks in blood insulin and creatine concentrations, and to maximise plasma insulin increase. The creatine, glucose and/or insulin or active derivatives of any of these may be infused into the blood in any suitable manner, for example by injection.

Further, the carbohydrate may be substituted or accompanied by insulin or an active derivative thereof. Ingestion or injection of compositions comprising creatine (or an active derivative thereof) and insulin (or an active derivative thereof) may be complimented by ingestion of carbohydrate, such as glucose, for example in the form of a drink. The timing of ingestion or injection (infusion) of the composition and carbohydrate is such that the increase in blood plasma carbohydrate concentration and insulin concentration and plasma creatine concentration peak substantially simultaneously.

Whilst endeavouring in the foregoing Specification to draw attention to those features of the invention believed to be of particular importance it should be understood that the Applicant claims protection in respect of any patentable feature or combination of features hereinbefore referred to and/or shown in the drawings whether or not particular emphasis has been placed thereon.

CLAIMS

1. A method of increasing creatine retention in the human or animal body by causing an increase in blood plasma creatine concentration and causing a substantially simultaneous increase in blood plasma insulin concentration.

2. A method according to claim 1, in which the plasma creatine concentration is increased by ingestion of creatine or an active derivative thereof.

3. A method according to claim 1, in which the plasma creatine concentration is increased by infusion of creatine.

4. A method according to any preceding claim, in which the plasma insulin concentration is increased by infusion of insulin or an active derivative thereof.

5. A method according to any of claims 1 to 3, in which the plasma

cause an increase in the blood plasma insulin concentration substantially simultaneously with the arrival in the plasma of the creatine.

10. A method according to any of claims 5 to 9, in which the creatine and/or agent is orally ingested.

11. A method of increasing glycogen storage in the human or animal body by causing an increase in blood plasma carbohydrate concentration and insulin concentration and causing a substantially simultaneous increase in blood plasma creatine concentration.

12. A method according to claim 11, in which the plasma creatine concentration is increased by ingestion and/or infusion of creatine or an active derivative thereof.

13. A method according to claim 11 or claim 12, in which the plasma carbohydrate and insulin concentrations are increased by ingestion and/or infusion of carbohydrate or an active derivative thereof.

14. A method according to claim 11 or claim 12, in which the plasma, glucose and insulin concentrations are increased by infusion of glucose or another simple carbohydrate.

15. A method according to any of claims 11 to 14, in which creatine or an active derivative thereof and glucose and/or another simple carbohydrate are orally ingested.

16. A composition for increasing creatine retention in the human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof.

17. A composition according to claim 16, in which the composition is in the nature of a dietary supplement.

18. A composition according to claim 16 or claim 17, in which the carbohydrate is glucose and/or another simple carbohydrate.

19. A composition according to any of claims 16 to 18, in which the composition comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

20. A method of increasing creatine retention in the human or animal body by ingestion of a composition as defined in any of claims 16 to 19.

21. A method as claimed in claim 20, in which the composition is ingested in an amount of 100g to 700g per day.

22. A method as claimed in claim 20 or claim 21, in which the composition is taken in four equal parts throughout the day.

23. A composition for increasing creatine retention in the human or animal body, the composition comprising creatine or an active derivative thereof together with insulin or a derivative thereof.

24. A composition for increasing glycogen storage in the human or animal body, the composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof.

25. A composition according to claim 23 or claim 24, in which the composition is in a form to be ingested and/or injected into the body.

26. A method of increasing creatine retention in the human or animal body by ingestion and/or injection of a composition as defined in any of claims 23 to 25.

27. A method of increasing glycogen storage in the human or animal

claims 23 to 25 above.

28. A method according to claim 26 or claim 27, in which a carbohydrate is also ingested and/or injected desirably such that an increase in blood plasma carbohydrate concentration and insulin concentration occurs substantially with an increase in blood plasma creatine concentration.

29. A composition for increasing glycogen storage in the human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof.

30. A composition according to claim 29, in which the composition is in the nature of a dietary supplement.

31. A composition according to claim 29 or claim 30, in which the carbohydrate is glucose and/or another simple carbohydrate.

32. A composition according to any of claims 29 to 31, in which the composition comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

33. A method of increasing glycogen storage in the human or animal body by ingestion and/or infusion of a composition as defined in any of claims 29 to 32.

34. A method according to claim 33, in which the composition is ingested in an amount of 100g to 700g per day.

35. A method according to claim 33 or claim 34, in which the composition is taken in four equal parts throughout the day.

36. A composition comprising creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use as an active

pharmaceutical composition.

37. A composition comprising creatine or an active derivative thereof and insulin or an active derivative thereof for use as an active pharmaceutical preparation.

38. A composition according to claim 37, in which the composition also comprises a carbohydrate or an active derivative thereof.

39. A composition comprising creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use in the manufacture of a substance for increasing creatine retention in the human or animal body.

40. A composition comprising creatine or an active derivative thereof, and insulin or an active derivative thereof, for use in the manufacture of a composition for increasing creatine retention and/or glycogen storage in the human or animal body.

41. A composition according to claim 40, in which carbohydrate or an active derivative thereof is also provided.

42. A composition comprising creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use in the manufacture of a substance for increasing glycogen storage in the human or animal body.

43. A composition according to claim 42, in which the carbohydrate is glucose and/or another simple carbohydrate.

44. A composition according to claim 42 or claim 43, in which the composition comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or a simple carbohydrate.

45. A method substantially as hereinbefore described with reference to the accompanying drawings.

46. A composition substantially as hereinbefore described with reference to the accompanying drawings.

47. Any novel subject matter or combination including novel subject matter disclosed, whether or not within the scope of or relating to the same invention as any of the preceding claims.

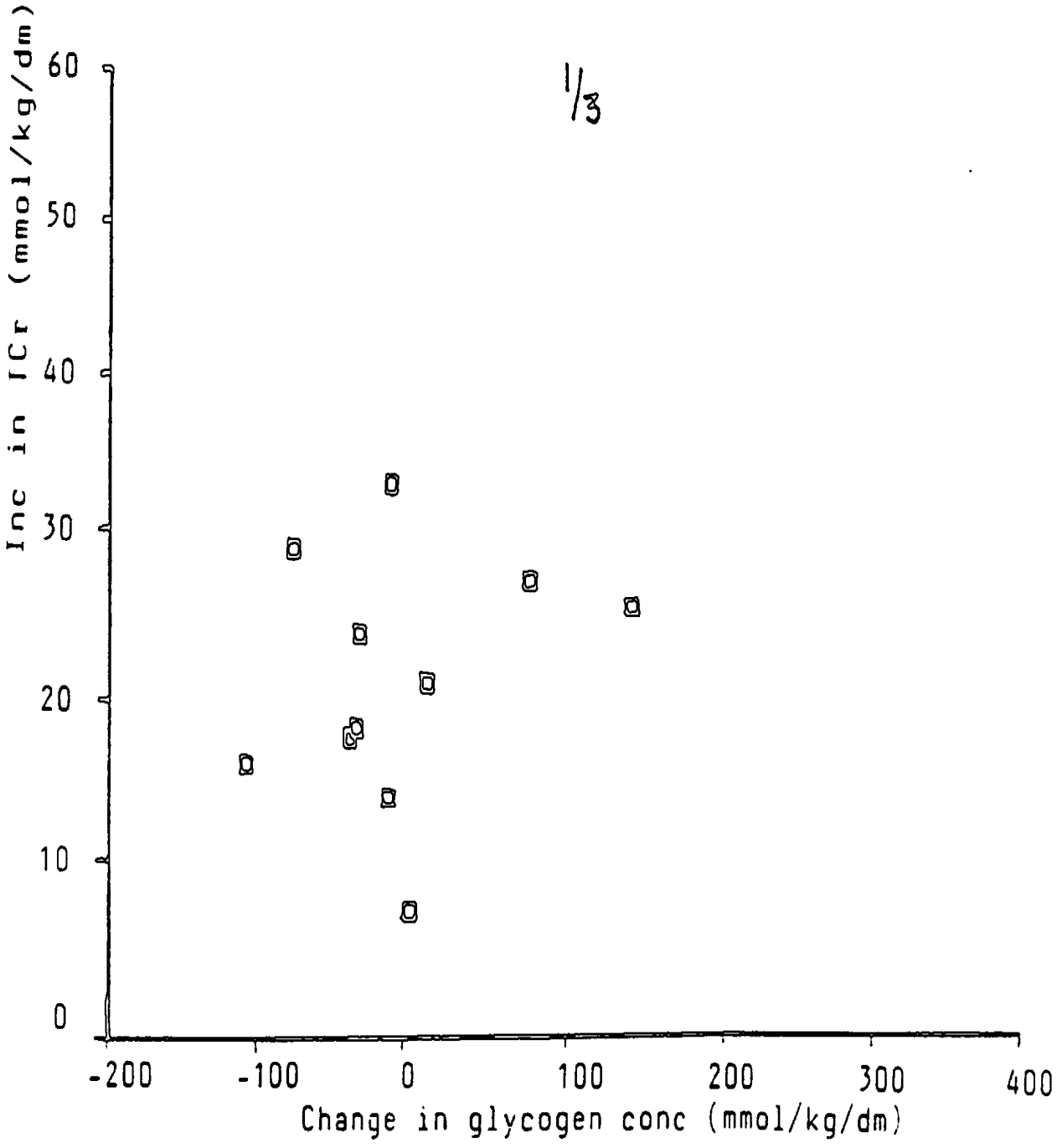
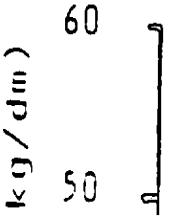

Inc in TCr (mmol/kg/dm)
60
50
40
30
20
10
0
-200
-100
0
100
200
300
400
Change in glycogen conc (mmol/kg/dm)

FIGURE 1


60
50

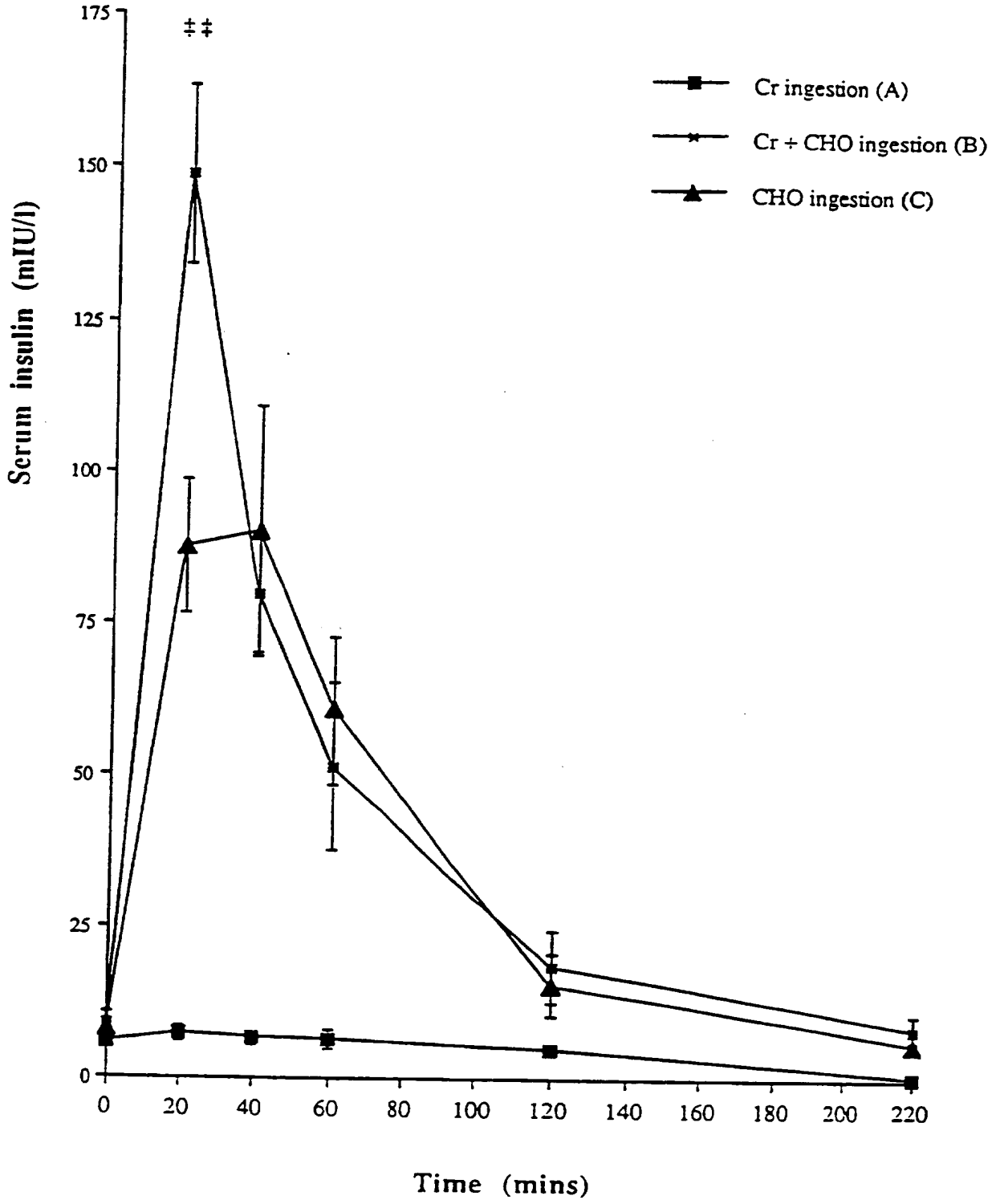
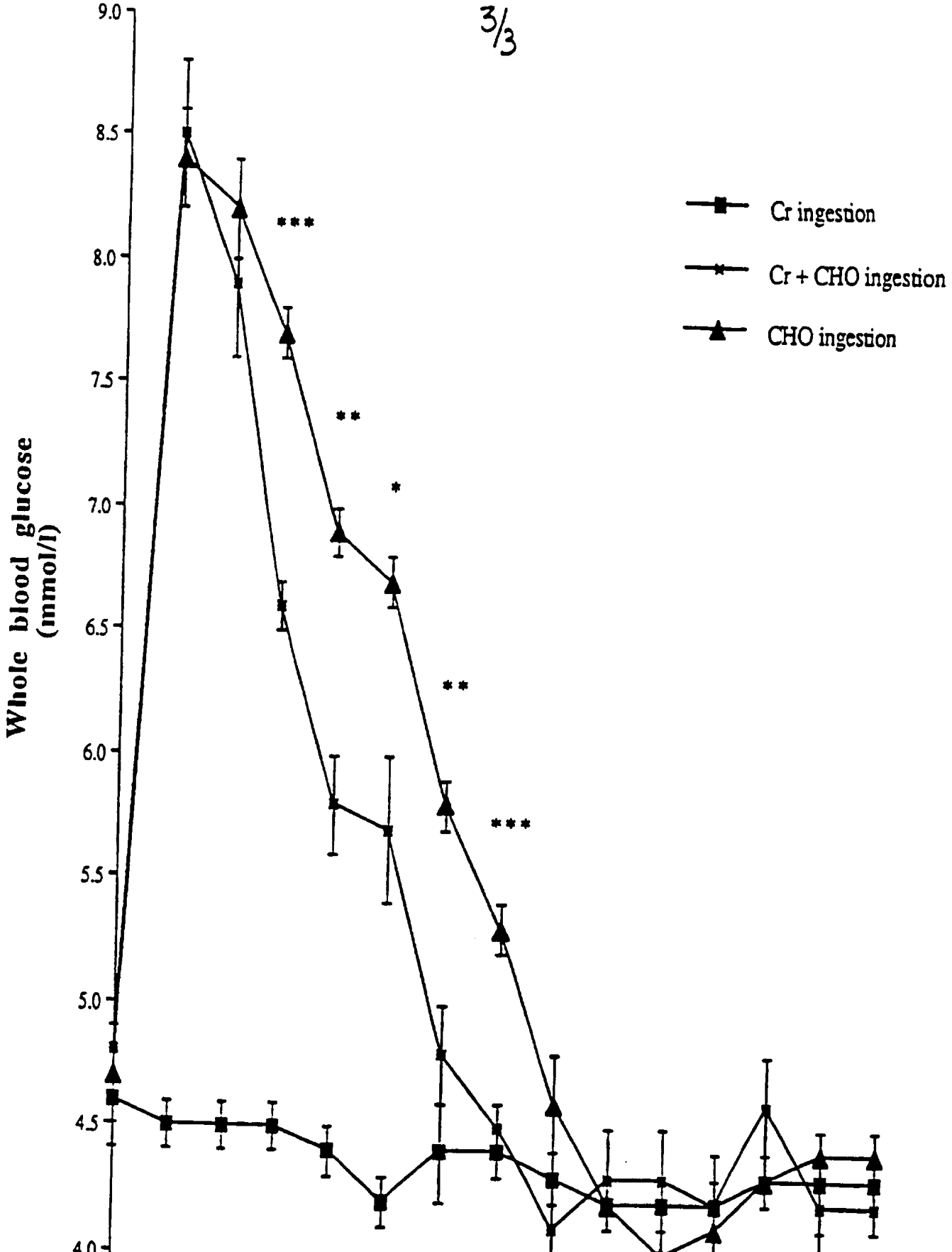

Serum insulin (mIU/l)
175
150
125
100
75
50
25
0
‡‡
Cr ingestion (A)
Cr + CHO ingestion (B)
CHO ingestion (C)
0
20
40
60
80
100
120
140
160
180
200
220
Time (mins)

FIGURE 3


Whole blood glucose (mmol/l)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
***
**
*
**
***
Cr ingestion
Cr + CHO ingestion
CHO ingestion

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/02933

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A23L1/305 A61K31/195 A61K31/70 A61K38/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 02127 (HULTMAN ERIC ;HARRIS ROGER C (GB)) 3 February 1994 see page 5, paragraph 1 see page 7, paragraph 4 ---	16,29, 36,39,42
X	EP,A,0 449 787 (SETRA SRL) 2 October 1991 see example 1 ---	16,29, 36,39,42
Y	ANON 'Pschyrembel - Klinisches Wörterbuch' 1990 , WALTER DE GRUYTER , BERLIN - NEW YORK see page 791 - page 791 see page 902 - page 903 ---	1-47
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 1996	02.04.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Bendl, E

Form PCT ISA 210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE EMBASE ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL HAIDER W. ET AL 'Improvement of cardiac preservation by preoperative high insulin supply' see abstract & J. THORAC. CARDIOVASC. SURG., 1984, 88/2 (294-300), USA, ---	1-47
Y	HEART CREATINE KINASE, (RES. SYMP.), 1980, 75-81, BESSMAN, SAMUEL P. 'The origin of the creatine-creatine phosphate energy shuttle' see page 80 -----	1-47

INTERNATIONAL SEARCH REPORT

[redacted]ernational application No.
PCT/GB95/02933

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1,11,20,26,27 and 33 are directed to a treatment of the human/animal body (see Rule 39.1 (iv) PCT) the search has been carried out and based on the alleged effects of the compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/02933

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9402127	03-02-94	AU-B-	4594893	14-02-94
		CA-A-	2140768	03-02-94
		EP-A-	0652748	17-05-95
		FI-A-	950302	24-01-95
		JP-T-	7509230	12-10-95
		NO-A-	950250	23-01-95
EP-A-0449787	02-10-91	IT-B-	1240336	07-12-93
		AT-T-	128360	15-10-95
		DE-D-	69113304	02-11-95